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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ORVILLE G. KOLTERMAN
and ANDREW A. YOUNG

Appeal 2009-002545[1]
Application 09/756,690
Technology Center 1600

Decided:[2] September 24, 2009

Before LORA M. GREEN, RICHARD M. LEBOVITZ, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for lowering triglyceride levels. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Amylin Pharmaceuticals, Inc., is the real party in interest.
[2] Oral argument was presented in this case on September 17, 2009.

We affirm.

STATEMENT OF THE CASE

Claims 1-15, 24-37, and 41 are pending and on appeal (App. Br. 2). Claim 1 is representative and reads as follows:

> 1. A method for lowering triglyceride levels in a subject in need thereof, comprising:
> identifying a subject having elevated postprandial triglyceride levels; and
> administering to said subject a therapeutically effective amount of an exendin or an exendin agonist, wherein said subject's postprandial triglyceride levels are lowered.

The Examiner cites the following documents as evidence of unpatentability:

Wagle et al.	US 6,326,396 B1	Dec. 4, 2001
Beeley et al.[3]	WO 98/30231 A1	Jul. 16, 1998

Frederik Karpe et al., *Differences in Postprandial Concentrations of Very-Low-Density Lipoprotein and Chylomicron Remnants Between Normotriglyceridemic and Hypertriglyceridemic Men With and Without Coronary Heart Disease*, 48 METABOLISM 301-307 (1999).

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 200-203, 2250 (Mark H. Beers et al. eds., 17th ed. 1999).

The following rejections are before us for review:

Claims 1-14, 24-36, and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Karpe and Beeley (Ans. 3-5).

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[3] The electronic filewrapper has two versions of the Beeley publication. The Examiner appears to cite the document stamped "CORRECT VERSION*" on the first page. We will do the same for consistency.

Claims 15 and 37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Karpe and Beeley as applied to claims 1- 14, 24-36 and 41, and further in view of Wagle (Ans. 5-6).

OBVIOUSNESS

ISSUE

The Examiner cites Karpe as disclosing that a postprandial[4] rise in plasma triglycerides "is more closely linked to the risk of developing coronary heart disease (CHD) than the fasting level, and that the plasma triglyceride concentration measured 6 hours after a mixed meal was associated with signs of early atherosclerosis in healthy men" (Ans. 3). The Examiner concedes that "Karpe does not teach a method for lowering triglyceride levels with an exendin" (*id.*).

To meet that deficiency, the Examiner cites Beeley as administering exendin or an exendin agonist in a therapeutic method that "is useful for, among others, reducing the cardiac risk . . . . Furthermore, Beeley teaches that the method is also useful for reducing appetite (food intake), reducing the weight of subjects, and lowering plasma lipid levels . . ., which comprise cholesterol and triglycerides" (*id.* at 4 (citing the Merck Manual 200 as evidence that plasma lipids included cholesterol and triglycerides)).

Based on these teachings, the Examiner concludes:

> [I]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to identify and to treat a subject having elevated postprandial triglyceride levels by administering an exendin or an agonist thereof following the method taught by Beeley in order to reduce the cardiac risk, as

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[4] "[T]he term 'postprandial' merely means after a meal" (Ans. 3).

> Karpe indicates that the postprandial elevation of plasma triglycerides is more closely linked to the risk of CHD.

(*Id.*)

The Examiner reasons that an ordinary artisan would have been motivated to perform the claimed steps to reduce and treat CHD risk, "and reasonably would have expected success because Beeley has taught that exe[n]din can reduce the cardiac risk, and that exe[n]din can lower plasma lipids, and control obesity (by reduce food intake), which are well known and important risk factors for in cardiovascular diseases" (*id.*).

The Examiner further reasons that, although the treatment would have been "implemented to a subject identified as one at . . . cardiac risk because of elevated postprandial triglyceride levels, it would be inherent that said subject's postprandial plasma triglyceride levels would be lowered, as the active ingredient, method steps and patient population would be the same as that of the present invention" (*id.* at 4-5).

Appellants contend that the Examiner "has failed to establish that one of ordinary skill in the art would have found it obvious to combine the teachings of Karpe *et al.* and Beeley *et al.*" (App. Br. 3.) Specifically, Appellants argue that Beeley "contains no teaching regarding the use of exendins to lower triglycerides. In fact, Beeley *et al*, does not mention triglycerides at all" (*id.* at 3-4).

Appellants further contend that it is known in the art that a therapeutic treatment affecting one plasma lipid component will not necessarily affect

another, and cite a number of publications[5] in support of that assertion, as well as a publication[6] purporting to show that administering one particular exendin results in lowered triglycerides in subjects with elevated triglycerides but not in subjects with normal triglycerides (*id.* at 5). Therefore, Appellants urge, "one of ordinary skill in the art would neither have expected exendins and exendin agonists to lower plasma triglyceride levels, nor have found it obvious to combine Beeley *et al.*'s exendins and exendin agonists with Karpe *et al.*'s subjects having elevated triglyceride levels" (*id.* at 4).

Appellants further argue that the Examiner erroneously posited that "subjects at cardiac risk inherently possess elevated triglyceride levels, and that methods of inhibiting food intake inherently lower plasma triglycerides" (*id.*). In this regard, Appellants argue, the Examiner failed to show that Beeley's methods of inhibiting food intake "necessarily lower plasma triglyceride levels[;] [i]n fact, evidence suggests that reducing food intake does not necessarily result in lowering triglyceride levels. For example, one

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[5] Giovanni Gaudio et al., *Changes in Plasma Lipids During Renin-Angiotensin System Blockade by Combination Therapy (Enalapril Plus Valsartan) in Patients With Diabetes and Hypertension*, 45 J. CARDIOVASC. PHARMACOL. 362-366 (2005); Inga-Stina Ödmark et al., *Effects of continuous combined conjugated estrogen/medroxyprogesterone acetate and 17β-estadiol/norethisterone acetate on lipids and lipoproteins*, 48 MATURITAS 137-146 (2004); Ali Saklamaz et al., *The beneficial effects of lipid-lowering drugs beyond lipid-lowering effects: A comparative study with pravastatin, atorvastatin, and fenofibrate in patients with type IIa and type IIb hyperlipidemia*, 54 METABOLISM CLINICAL AND EXPERIMENTAL 677-681 (2005); Haffner et al., *Management of Dyslipidemia in Adults With Diabetes* 26 DIABETES CARE 583-586 (Supp. 1, 2003).

[6] Kim et al., 23 DIABETIC CARE 608-753, Abstract P1946 (Supp. 4, 2006).

review article indicates that a reduction in food intake left triglyceride levels unchanged but lowered other plasma lipid levels" (*id.* (citing Bravata[7])).

Instead, Appellants contend, the Examiner's application of inherency "is based on hindsight. The Office has used the knowledge from appellants' disclosure that an exendin or an exendin agonist lowers plasma triglyceride levels as a roadmap to combine Beeley *et al.*'s exendins and exendin agonists with Karpe *et al.*'s subjects having elevated triglyceride levels" (*id.* at 6).

Appellants do not argue the claims subject to this ground of rejection separately. We select claim 1 as representative of the rejected claims. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Accordingly, in view of the positions advanced by Appellants and the Examiner, the issue with respect to this rejection is whether Appellants have shown that the Examiner erred in concluding that an ordinary artisan would have considered claim 1 prima facie obvious in view of Karpe and Beeley.

FINDINGS OF FACT ("FF")

1. Karpe discloses a study on the relationship between postprandial triglyceride levels and coronary heart disease ("CHD") (Karpe 301). Karpe states:

> It has been suggested that the postprandial elevation of plasma triglycerides is more closely linked to CHD than the fasting level. Patsch and et al found that plasma triglycerides measured 6 to 8 hours after a large high-fat meal were highly discriminative for CHD among normotriglyceridemic (NTG) individual. This finding was later confirmed by others. Furthermore, we recently found that the plasma triglyceride

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[7] Dena M. Bravata et al., *Efficacy and Safety of Low-Carbohydrate Diets*, 89 JAMA 1837-1850 (2003).

> concentration measured 6 hours after a mixed meal was associated with signs of early atherosclerosis in healthy men examined by carotid artery B-mode. This association was independent of plasma low-density lipoprotein (LDL) cholesterol and fasting plasma triglycerides.

(*Id.* (citations omitted).)

2. Karpe discloses that "[t]he present study confirms previous observations that plasma triglycerides measured late in the postprandial state (well beyond the peak level) are discriminative for CHD, in contrast to fasting plasma triglycerides and adds to the mechanistic framework of this finding" (*id.* at 306 (citations omitted)).

3. Beeley discloses "the surprising discovery that exendins and exendin agonists have a profound and prolonged effect on inhibiting food intake" (Beeley 7). Based on this discovery, Beeley further discloses "methods for treating conditions or disorders associated with hypernutrition, comprising the administration of an exendin" (*id.*).

4. Beeley discloses that in certain "preferred aspects, a method is provided for lowering plasma lipids comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist" (*id.* at 10).

5. Beeley also discloses that "[t]he methods of the present invention may also be used to reduce the cardiac risk of a subject comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist" (*id.*).

6. The Merck Manual discloses, and Appellants do not dispute, that the major plasma lipids include cholesterol and triglycerides (Merck Manual 200).

7. Appellants cite Bravata as disclosing "that a reduction in food intake left triglyceride levels unchanged but lowered other plasma lipid levels" (App. Br. 4). The Examiner does not dispute this characterization of Bravata's disclosure.

8. Appellants cite Gaudio as disclosing that "a combination of enalapril and valsartan reduced total cholesterol and LDL levels, increased HDL levels, and [yet] had no effect on triglyceride levels in patients with diabetes and hypertension" (*id.* at 5). The Examiner does not dispute this characterization of Gaudio's disclosure.

9. Appellants cite Ödmark as disclosing that "hormonal replacement resulted in significant lowering of total cholesterol, HDL and LDL levels, without any significant changes in triglyceride levels" (*id.*). The Examiner does not dispute this characterization of Ödmark's disclosure.

10. Appellants cite Saklamaz as disclosing "the failure of pravastatin, a[n] HMG-CoA reductase inhibitor, to lower plasma triglyceride levels while lowering LDL levels," thus showing that "[e]ven in patients with hyperlipidemia, lipid-lowering drugs differentially affect lipid" (*id.*). The Examiner does not dispute this characterization of Saklamaz's disclosure.

11. Appellants cite Haffner as disclosing that "that a class of compounds known as bile acid binding resins lower LDL levels, but increase plasma triglyceride levels" (*id.*). The Examiner does not dispute this characterization of Haffner's disclosure.

12. Appellants cite Kim as disclosing that "treatment with exenatide (exendin-4) resulted in significant reductions in triglycerides in subjects having elevated triglycerides prior to the initiation of treatment (baseline triglycerides), but that no significant changes were observed in subjects

whose baseline triglycerides were normal" (*id.* n. 1). The Examiner does not dispute this characterization of Kim's disclosure.

13. The Specification discloses that "exendins and exendin agonists have a significant effect on the reduction of blood serum triglyceride concentrations" (Spec. 10).

PRINCIPLES OF LAW

As the Supreme Court pointed out in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Rather, the Court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added.)

While the Court acknowledged the importance of providing a rationale for practicing the claimed subject matter, the Court noted that "[i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *Id.* at 419.

Ultimately therefore, as our reviewing court has stated, "[i]n determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references

would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

ANALYSIS

Appellants' arguments do not persuade us that the Examiner erred in concluding that an ordinary artisan would have considered claim 1 prima facie obvious. Rather, we agree with the Examiner that Karpe and Beeley would have suggested practicing the claimed process.

Claim 1 recites a method for lowering triglyceride levels in a subject in need thereof. The method has two steps: (1) identifying a subject having elevated postprandial triglyceride levels, and (2) administering a therapeutically effective amount of an exendin or an exendin agonist to the subject. Administering the exendin lowers the subject's postprandial triglyceride levels.

Karpe discloses that an elevated postprandial triglyceride level is discriminative in identifying subjects with coronary heart disease ("CHD") (FF 2). Thus, Karpe would have suggested to an ordinary artisan that performing the first step in the claimed process, identifying a subject having elevated postprandial triglyceride levels, was a desirable method of identifying subjects at risk and in need of treatment for CHD.

Beeley discloses that administering exendins or exendin agonists is an effective method of reducing cardiac risk (FF 5). Thus, Beeley would have suggested to an ordinary artisan that performing the second step recited in claim 1, administering a therapeutically effective amount of an exendin to a subject identified as having elevated triglycerides, would be a desirable method of treating the patient population identified by Karpe's methods.

Therefore, because Karpe discloses the desirability of identifying the population of patients recited in the first step of claim 1, and because Beeley discloses the desirability of treating that population of patients by administering the same therapeutic agent recited in the second step of claim 1, we agree with the Examiner that the ordinary artisan would have had sufficient reason to combine the teachings of both Karpe and Beeley.

It might be true that Appellants' stated purpose for performing the claimed method, reducing triglycerides, is a slightly different reason than Beeley's more general purpose of treating coronary heart disease risk. However, it is well settled claimed subject must be considered prima facie obvious when the prior art suggests its practice, even if the prior art's rationale differs from applicant's. *See KSR*, 550 U.S. at 419.

We agree that exendins' inherent capacity to reduce triglycerides in patients with elevated triglycerides is disclosed in Appellants' Specification (FF 13). However, given that the suggestion to practice exactly the steps recited in claim 1 is derived from the references' disclosures rather than any unknown property, we are not persuaded that the Examiner failed to correctly apply the principles of inherency, or arrived at the claimed invention through improper hindsight.

We acknowledge that a prima facie case of obvious cannot be *based* on a fact not disclosed in the prior art. *See In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.' Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection.") (quoting *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966)).

As discussed above, however, in the instant case the Examiner does not use the inherent triglyceride-lowering properties of exendins to bridge the difference between claim 1 and the references, or to provide the suggestion for performing the steps in claim 1. Rather, the Examiner points to the inherency of exendins' triglyceride-lowering properties to show that performing the claimed steps, as the references suggest, would have necessarily resulted in the triglyceride-lowering effect recited in the last clause of claim 1. *Cf. In re Woodruff*, 919 F.2d 1575, 1577-78 (Fed. Cir. 1990) (obviousness rejection of method claim affirmed where performing claimed process necessarily resulted in claim-recited effect).

We acknowledge the undisputed facts that lowering food intake and administering lipid-lowering agents do not uniformly reduce triglyceride levels (*see* FF 7-11). However, as discussed above, the prior art-suggested purpose of administering exendins is to treat the cardiac risk identified by elevated triglycerides, not to *per se* lower the elevated triglycerides.

Thus, given Beeley's affirmative disclosures that exendins treat cardiac risk and lower plasma lipid levels (FF 4, 5), we are not persuaded that the lack of absolute predictability in reducing triglyceride levels would have undermined an ordinary artisan's reasonable expectation that following Beeley's teachings would result in the disclosed therapeutic effect against cardiac risk or coronary heart disease.

We also acknowledge the undisputed fact that exendins only appear to work in subjects having elevated, as opposed to normal, triglyceride levels (FF 12). Karpe nonetheless teaches identifying exactly that set of individuals as being at risk for coronary heart disease (FF 1, 2), and Beeley teaches that individuals at risk for coronary heart disease should be treated

with exendins (FF 4). We are therefore not persuaded that the efficacy of exendins only in patients with high triglycerides undermines the Examiner's prima facie case.

In sum, Appellants' arguments do not persuade us that the Examiner erred in concluding that the subject matter of claim 1 would have been obvious to a person of ordinary skill in the art. As Appellants point to no evidence of unexpected results sufficient to rebut the Examiner's prima facie case, we affirm the rejection of claim 1, as well as claims 2-14, 24-36, and 41, which were not argued separately. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claims 15 and 37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Karpe and Beeley as applied to claims 1-14, 24-36 and 41, and further in view of Wagle (Ans. 5-6). The Examiner cites Wagle to meet the limitation in claims 15 and 37 requiring the exendin or exendin agonist to be used "in combination with a statin for lowering triglyceride levels" (*id.* at 5).

Specifically, the Examiner cites Wagle as disclosing that "HMG-CoA reductase inhibitors (also known as 'statins') are agents acting directly on plasma triglyceride and cholesterol content, and are effective in lowering triglyceride and cholesterol content, and that lowering of circulating lipids has been to reduce the cardiovascular morbidity" (*id.*). The Examiner concludes that an ordinary artisan would have considered it obvious to combine Beeley's exendins with Wagle's statins "because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for the same purpose of lowering plasma lipid" (Ans. 6).

Appellants do not dispute the Examiner's characterization of Wagle's disclosure. Rather, Appellants argue only that

> Whatever else Wagle *et al* discloses, it too does nothing to remedy the deficiencies of Karpe *et al* and Beeley *et al*. Additionally the Office has provided no evidence or reasoning why one skilled in the art would combine these references, especially when they address such divergent molecules to arrive at the presently claimed invention.

(App. Br. 7.)

We are not persuaded by these arguments.

The Examiner explicitly states that an ordinary artisan would have been "motivated to [combine Wagle's statins with Beeley's exendins] because Wagle teaches that lowering plasma triglyceride and cholesterol is beneficial for reducing the cardiovascular morbidity, and reasonably would have expected success because both drugs had been demonstrated in the prior art to be effective on lowering plasma lipid" (Ans. 6).

Thus, contrary to Appellants' assertion, the Examiner did in fact provide reasoning -- the common patient populations treatable by the drugs -- as to why an ordinary artisan would have combined them. In contrast, Appellants have provided no evidence suggesting that an ordinary artisan would have considered the claimed combination unsuitable, or that it would have failed to treat the patients in question.

Because Appellants have failed to show that the Examiner erred in concluding that claims 15 and 37 would have been obvious to a person of ordinary skill in the art, we affirm the Examiner's rejection of those claims as obvious over Karpe, Beeley, and Wagle.

SUMMARY

We affirm the Examiner's rejection of claims 1-14, 24-36, and 41 under 35 U.S.C. § 103(a) as being unpatentable over Karpe and Beeley.

We also affirm the Examiner's rejection of claims 15 and 37 under 35 U.S.C. § 103(a) as being unpatentable over Karpe, Beeley and Wagle.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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